

## REMARKS

### Status of the Application

The Applicants gratefully acknowledge the Examiner's withdrawal of the rejections, raised under 35 U.S.C. §102 and 35 U.S.C. §112 first paragraph, of pending claims 1 and 4.

Claims 1 and 4 remain pending in the instant application.

Claims 1 and 4 are rejected on the following ground:

1. Claims 1 and 4 stand rejected under 35 U.S.C. §103(a) as being unpatentable, in view of obviousness, over U.S. patent 4,762,779 to Snitman in view of U.S. patent 6,255,476 to Vinayak *et al.*

The Applicants believe the following remarks traverse the Examiner's rejection of the claims.

### The Claims Are Not Obvious Under 35 U.S.C. 103(a)

#### A. The Examiner Fails to Make A *Prima Facie* Case of Obviousness

Claims 1 and 4 stand rejected as allegedly unpatentable over Snitman, in view of Vinayak *et al.*. The Examiner is reminded that a *prima facie* case of obviousness requires citation to a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitle the Applicants to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Applicants respectfully submit the Examiner has failed to establish any of the three elements of a *prima facie* case of obviousness.

**1. No Motivation to Combine the References**

A proper analysis, in view of 35 U.S.C. 103, demands the references cited by the Examiner be considered as whole and must suggest the desirability and, thereby, the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submits that references cannot be considered collectively until the Examiner points to some motivation to combine said references. This analysis prevents the Examiner from using the instant specification to reconstruct, in hindsight, the invention as claimed. The Federal Circuit has articulated the policy behind this analysis:

"To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

See: *In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

The prior art, referenced above, does not suggest the desirability of making the combination of elements which recapitulates the invention as claimed. In the Office Action mailed on February 13, 2006 the Examiner stated,

"[i]t would have been obvious to one of ordinary skill the art to combine teaching of both Snitman and Vinayak and reach the method of labeling oligonucleoties using the claimed bifunctional linker."<sup>1</sup>

The Applicants respectfully submit the Examiner presents bald conclusions in place of reasoned motivation, as demanded by the Federal Circuit, to combine the cited art.

Specifically the section of the '476 patent to Vinayak *et al.*, cited by the Examiner in the pending rejection under 35 U.S.C. 103, merely recites a list (e.g. methyl, lower alkyl, substituted alkyl, phenyl, aryl, and substituted aryl) of oxygen protecting groups or substituent for the "R"

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<sup>1</sup> Office Action mailed February 13, 2006, p. 4.

substitution of specific protected-amino phosphoramidites. This alleged teaching by Vinayak *et al.*, however, does not disclose (nor suggest) the advantages offered by the *specific bifunctional linkers* used in the labeling methods as claimed in the pending application. Despite this shortcoming, the Examiner attempts to fill the void left by the deficient art of Snitman and Vinayak *et al.* with a conclusory argument regarding the alleged "obvious" adaptation of the prior art cited. Specifically, the Examiner sets out the proposition that,

"The ordinary artisan would have been motivated to do so because using any moiety at that position that could undergo beta-elimination would have worked for the method taught by Snitman. As such, the methyl is an equivalent of the CH<sub>2</sub>CH<sub>2</sub>CHN. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to use CH<sub>2</sub>CH<sub>2</sub>CHN instead of methyl group for the bifunctional liker. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made."<sup>2</sup>

The *Rouffet* court, however, admonishes against such an unsupported statement. Indeed, the Federal Circuit stated:

"The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *Rouffet*, 47 USPQ2d at 1458.

Contrary to the Examiner's opinion, the prior art provides no motivation to combine the references to teach the claimed invention which describes, in part, the use of *specific bifunctional*

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<sup>2</sup> *Id.*

*linkers* and *in situ activated labels* in methods which produce a labeled support-bound protected oligonucleotide. Accordingly, the rejection of claims 1 and 4, under 35 U.S.C. 103(a) should be withdrawn.

## 2.      **There Is No Parity Of Elements**

The Examiner alleges the methyl groups taught in the cited art render obvious the CH<sub>2</sub>CH<sub>2</sub>CHN moiety comprising the bifunctional linkers recited in the methods as claimed. To rebut the Examiner's assertion the Applicants file, herewith, the "Declaration of Dr. Gabriel Alvarado Filed Pursuant To 37 C.F.R. § 1.132". At paragraph four of his declaration, Dr. Alvarado states the two methoxy cyanoethyl moiety, which comprise the bifunctional linkers as claimed, were selected only after empirical experimentation. This experimentation alone is evidence of the non-obviousness of the linkers as claimed.

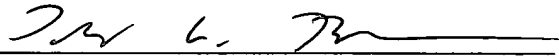
Notwithstanding the observation that the claim linkers were empirically derived, Dr. Alvarado also notes, at paragraph five of his declaration, that use of the methyl groups described by Snitman, in the methods as claimed, would result in a decrease in the efficiencies and yields of the claimed reactions. Moreover, as noted in paragraph six of Dr. Alvarado's declaration, nothing in the teachings set out in U.S. patent 4,762,779 to Snitman and / or U.S. patent 6,255,476 to Vinayak *et al.* would suggest the use linkers, comprising CH<sub>2</sub>CH<sub>2</sub>CHN, which facilitate the reactions in the claimed embodiments of present invention.

In sum, the Applicants note that even if improperly combined the cited art fails to teach all the elements of the methods as claimed. Moreover, the Applicants provide a fact-based declaration which rebuts the Examiner's pending rejections based on the obviousness of the claimed embodiment of the present invention in view of the cited art. Having provided such a declaration, the Examiner is obliged to consider the same. See, MPEP 716.01(d) and *In re Orfeo*, 169 USPQ 487, 489 (C.C.P.A. 1971).

**CONCLUSION**

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourages the Examiner to call the undersigned collect at (617) 984-0616.

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